

Evaluation and Management of Gallstone-Related Diseases in Non-Pregnant Adults

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Patient Population: Adult patients with suspected or confirmed biliary colic, acute cholecystitis, choledocholithiasis, cholangitis, or mild gallstone pancreatitis. Excluded are patients who: are pregnant patients, have a history of bypass surgery or biliary surgery, or have acute pancreatitis. For these conditions, consult appropriate subspecialists.

Objectives: Create an evidence-based guideline for the management of gallstone-related diseases that provides prompt and appropriate service to patients, reduces unnecessary diagnostic testing, and improves patient outcomes.

Key Points

Clinical Presentation. Patients presenting with upper abdominal pain or jaundice should be evaluated for gallstone-related disease.

Diagnosis.

The evaluation for gallstone-related disease is summarized in **Table 1**. The evaluation routinely includes:

1. Complete physical exam
2. Laboratory evaluation – CBC, comprehensive metabolic panel, lipase
3. Imaging – Right upper quadrant (RUQ) ultrasound

For most patients with acute cholecystitis, diagnosis can be based on history, physical findings, laboratory tests, and ultrasound (see **Table 3** for the sonographic diagnostic criteria). In rare cases where the diagnosis remains uncertain after this evaluation, additional imaging modalities may be necessary.

Treatment.

The treatment of gallstone-related diseases is summarized in the **Figure**.

Biliary Colic

- Minimally symptomatic or with symptoms that resolve: provide reassurance, education on avoidance of triggers (eg, dietary fat). Provide direct referral to elective surgery (General Surgery clinic for surgery within 2 weeks at University of Michigan). [II-C*]
- Moderate to severe symptoms: consult surgery. Perform non-urgent laparoscopic/open cholecystectomy during same visit [II-C*]. Timing of surgery determined by patient preference and operating room availability.

Acute Cholecystitis

- Admit to Surgery
- Initiate IV antibiotics (**Table 2**)
- Perform laparoscopic/open cholecystectomy within 24-48 hours [I-A*].
 - In patients without gallstones who have right upper quadrant (RUQ) and/or epigastric pain and a hepatobiliary iminodiacetic acid (HIDA) scan showing delayed gallbladder filling or lack of gallbladder emptying, cholecystectomy should be recommended [I-A*].
 - For patients deemed to be poor surgical candidates, nonsurgical gallbladder drainage procedures are recommended (**Figure 2**)

Choledocholithiasis

Choledocholithiasis may occur alone, but should also be considered as a comorbidity with cholecystitis or any of the other gallstone-related diseases.

- Evaluate for evidence of cholangitis (**Table 5**). If suspected, treat as cholangitis (see below).
- If no evidence of cholangitis, admit to surgery and prepare for cholecystectomy.
- If choledocholithiasis is demonstrated on imaging, preoperative ERCP is often performed to clear the duct.
- If choledocholithiasis is not documented on imaging, estimate the likelihood of choledocholithiasis (**Table 4**)
 - Low likelihood: no additional evaluation is needed, and routine intraoperative cholangiography (IOC) is not recommended [III-B]

- **Intermediate likelihood:** recommended approach is a one-stage procedure with laparoscopic cholecystectomy with IOC within 24 to 48 hours of admission (24 hours preferred). [I-A*] Alternate approaches might include preoperative imaging with ERCP or MRCP, especially if IOC will not be performed.

NOTE: If intraoperative cholangiogram (IOC) demonstrates a retained common bile duct (CBD) stone:

- Perform procedure to remove CBD stones during the same operation [I-A*], or
- Obtain gastroenterology consult within 24 hours after surgery for endoscopic retrograde cholangio-pancreatography (ERCP).
- **High likelihood:** preoperative ERCP is often performed to clear the duct.

Cholangitis

- Admit to Medicine service.
- Initiate IV antibiotics, NPO (**Table 2**).
- Obtain Gastroenterology consult.
- Classify severity of acute cholangitis (**Table 6**).
 - Mild cholangitis with adequate response to medical therapy: ERCP within 72 hours.
 - Moderate-severe or not responsive to medical therapy: ERCP within 24 hours.
- Consult Surgery for laparoscopic/open cholecystectomy during same admission, after cholangitis resolves.

Gallstone Pancreatitis: Evaluate for evidence of cholangitis (**Table 5**). If suspected, treat as cholangitis (see above), otherwise classify severity of gallstone pancreatitis (Table 7).

Mild gallstone pancreatitis:

- Admit to surgery service.
- Perform laparoscopic/open cholecystectomy with IOC within 24 (preferred) to 48 hours [I-B*].
- If IOC demonstrates a retained CBD stone:
 - Surgical removal of CBD gallstone [I-A*], - or -
 - Gastroenterology consult for ERCP within 24 hours of surgery.

Moderate to severe gallstone pancreatitis:

- Admit to medicine.
- Consider gastroenterology consultation, and preoperative ERCP if bilirubin is elevated or cholangitis present.
- Delay cholecystectomy until pancreatitis resolves.

NOTE: For detailed management of acute pancreatitis at the University of Michigan: <http://pancmap.med.umich.edu/>

* Strength of recommendation:

I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.

Levels of evidence reflect the best available literature in support of an intervention or test:

A = systematic reviews of randomized controlled trials with or without meta-analysis, B = randomized controlled trials, C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control), D = individual observation studies (case study/case series), E = expert opinion regarding benefits and harm

Table 1. Clinical Features of Gallstone-Related Diseases

Gallstone-Related Diseases*	Clinical Features
Biliary Colic	<p><u>H&P:</u> Severe, episodic, epigastric or RUQ pain; may be nocturnal, occasionally postprandial. +/- RUQ tenderness.</p> <p><u>Labs:</u> No leukocytosis; normal total bilirubin and amylase/lipase.</p> <p><u>Imaging:</u> RUQ ultrasound indicating cholelithiasis <i>without</i> findings of cholecystitis (Table 3).</p>
Acute Cholecystitis	<p><u>H&P:</u> +/- fever; symptoms persist or worsening; positive for RUQ tenderness.</p> <p><u>Labs:</u> Leukocytosis is common. Total bilirubin is usually normal to mildly elevated (<2.0 mg/dL), unless there is concomitant choledocholithiasis. Amylase and lipase are usually normal unless there is concomitant pancreatitis.</p> <p><u>Imaging:</u></p> <ul style="list-style-type: none"> • RUQ ultrasound, see Table 3. The diagnosis of cholecystitis is NOT made based on ultrasound findings alone. Diagnosis is determined based on the clinical findings above, in combination with consistent ultrasound findings. • HIDA (only indicated if RUQ ultrasound is inconclusive, or contradicts the clinical impression) demonstrates lack of gallbladder filling.
Choledocholithiasis	<p><u>H&P:</u> Biliary pain, jaundice, no fever.</p> <p><u>Labs:</u> Elevated bilirubin (total bilirubin often >2.0 mg/dL). Amylase/lipase are usually normal, unless there is concomitant pancreatitis.</p> <p><u>Imaging:</u> RUQ ultrasound shows CBD dilation (>7 mm).**</p> <p><u>Risk Stratification:</u> See Table 4.</p>
Cholangitis	<p><u>H&P:</u> Jaundice, often febrile, RUQ tenderness.</p> <p><u>Labs:</u> Elevated bilirubin (total bilirubin >2.0 mg/dL), leukocytosis. Amylase/lipase are usually normal to mildly elevated, unless there is concomitant pancreatitis.</p> <p><u>Imaging:</u> RUQ ultrasound: CBD dilation (>7 mm).**</p> <p><u>Diagnosis and risk stratification:</u> See Tables 5 & 6.</p>
Gallstone Pancreatitis	<p><u>H&P:</u> +/- jaundice, +/- fever, epigastric tenderness.</p> <p><u>Labs:</u> Normal or elevated bilirubin, elevated amylase and/or lipase to typically 3x upper limit of normal. Elevated ALT >150 suggests a biliary cause of pancreatitis, based on meta-analysis¹</p> <p><u>Imaging:</u> RUQ ultrasound: Cholelithiasis and biliary dilation variably present. Note: RUQ ultrasound is often limited for the evaluation of the pancreatic parenchyma.</p> <p><u>Absence of other common causes of pancreatitis:</u> Ethanol abuse, hyperglycemia, hypertriglyceridemia, hypercalcemia, or medications known to cause pancreatitis.</p> <p><u>Classification of pancreatitis severity:</u> see Table 7.</p>

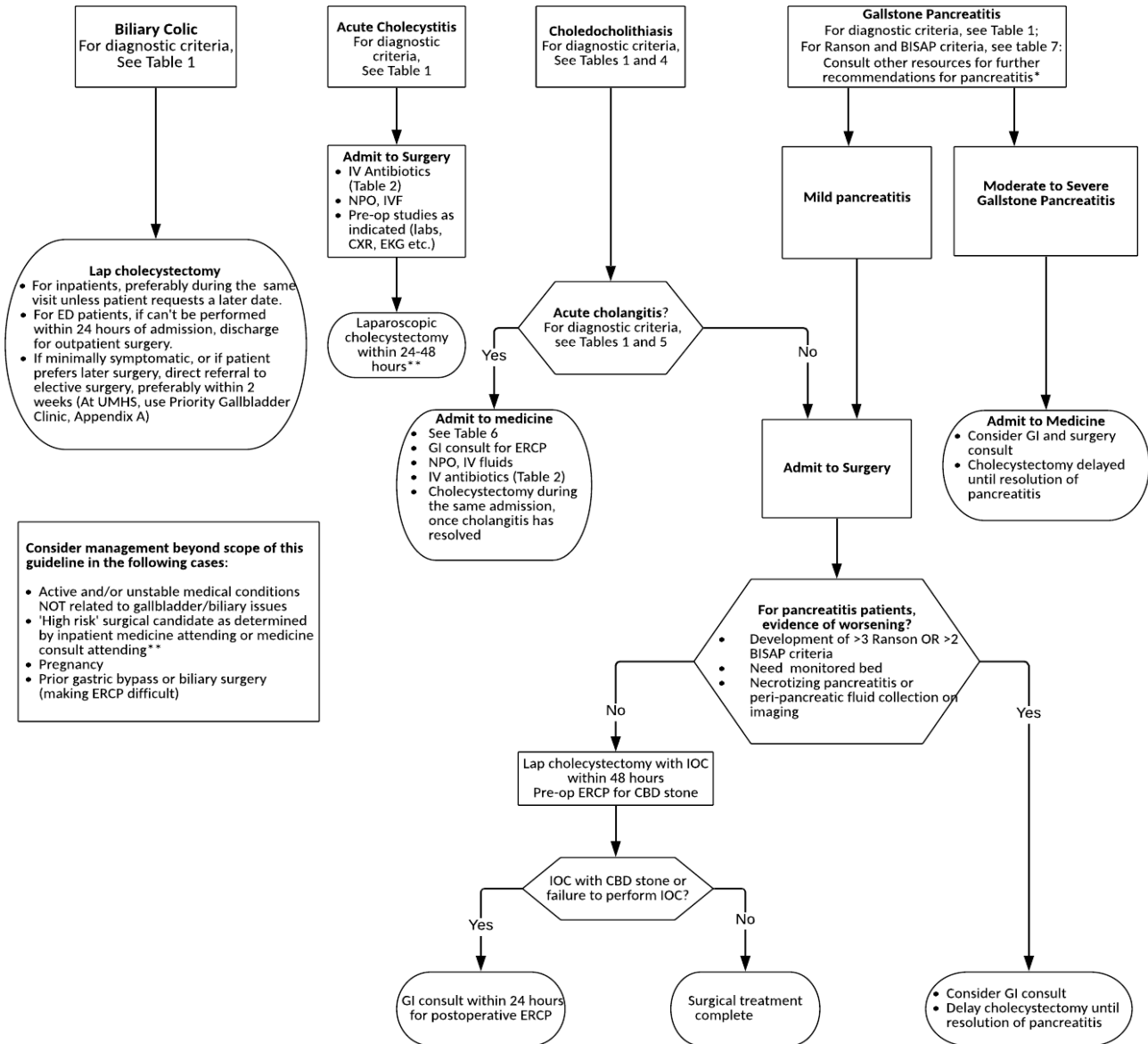
RUQ: Right upper quadrant; HIDA: hepatobiliary iminodiacetic acid; CBD: common bile duct; ALT: alanine aminotransferase

*These diseases are not mutually exclusive and often present together. For example, patients with choledocholithiasis often present with gallstone pancreatitis.

**Post-cholecystectomy patients may have CBD dilation in the absence of biliary pathology

Note: upper abdominal pain, nausea, and vomiting (N/V) are common to all of these disorders

Figure 1: Treatments for Gallstone-Related Diseases



Note: These conditions are not mutually exclusive. For example, patients with cholecystitis may also have CBD stones or cholangitis.

*For University of Michigan, consult <http://pancmap.med.umich.edu/>.

**For acute cholecystitis patients who are poor surgical candidates refer to page 13 for options.

AST = Aspartate Aminotransferase/ Aspartate Transaminase; BUN = Blood Urea Nitrogen; CXR = Chest radiograph; EKG = Electrocardiogram; ERCP = Endoscopic Retrograde Cholangiopancreatography; HR = Heart rate; IOC = Intraoperative cholangiogram; NPO = Nils per os/nothing by mouth; WBC = White blood cell count.

Table 2. Antibiotic Guidelines for Treatment of Cholecystitis and Cholangitis in Adults

Empiric Antibiotic Therapy	
<u>Community-acquired, without severe sepsis/shock</u>	
<ul style="list-style-type: none"> ○ 1st line: Cefuroxime¹ 1.5 g IV q8h +/- metronidazole 500 mg PO/IV q8h (if anaerobic coverage required²) ○ <u>High-risk allergy³/contraindications⁴ to beta-lactams</u>: Ciprofloxacin* 400 mg IV q8h +/- metronidazole 500 mg PO/IV q8h (if anaerobic coverage is required²) 	
<u>Community-Acquired with severe sepsis⁵/shock⁶ OR MDR-GNR risk⁷</u>	
<ul style="list-style-type: none"> ○ 1st line: Piperacillin-tazobactam¹ 4.5 g IV q6h ○ <u>Low/medium-risk allergy⁸ to penicillins</u>: Cefepime¹ 2 g IV q8h + metronidazole 500 mg PO/IV q8h <ul style="list-style-type: none"> ○ Consider the addition of vancomycin to cefepime for enterococcus coverage in critically ill patients with risk factors for enterococcal infection⁹. ○ <u>High-risk allergy³/contraindication⁴ to beta-lactams</u>: Vancomycin¹ + aztreonam¹ 2 g IV q8h + metronidazole 500 mg PO/IV q8h 	
Stepdown Antibiotic Therapy	
<p>Step-down oral therapy can be used if the patient is tolerating oral intake, and susceptibilities (if available) do not demonstrate resistance</p> <ul style="list-style-type: none"> ○ Amoxicillin-clavulanic acid¹ 875 mg PO BID, OR ○ Cefuroxime¹ 500 mg PO BID +/- metronidazole 500mg PO TID (if anaerobic coverage required²) ○ <u>High-risk allergy³/contraindications⁴ to beta-lactams OR MDR-GNR risk⁷</u>: Ciprofloxacin 750 mg PO BID +/- metronidazole 500 mg PO TID (if anaerobic coverage required²) 	
Duration of Antibiotic Therapy	
<ul style="list-style-type: none"> ○ In general: 4-7 days² ○ After cholecystectomy: Discontinue within 24 hours unless evidence of infection outside the gallbladder wall ○ After successful ERCP: 4 days post-procedure ○ Patients with bacteremia: 7-14 days. For patients with secondary gram-negative bacteremia, a 7-day duration of IV therapy (or oral quinolone at discharge) may be appropriate for selected patients, in conjunction with ID consultation. ○ Duration of therapy may be extended with inadequate source control or persistent clinical symptoms or signs of infection. 	

¹ Adjust dose based on renal function

² Anaerobic coverage (metronidazole) is not necessary for patients with community-acquired cholecystitis/cholangitis of mild-moderate severity, unless a biliary-enteric anastomosis is present.

³ High-risk allergies include: respiratory symptoms (chest tightness, bronchospasm, wheezing, cough), angioedema (swelling, throat tightness), cardiovascular symptoms (hypotension, dizzy/lightheadedness, syncope/passing out, arrhythmia), anaphylaxis

⁴ Previous reactions that are contraindications to further beta-lactam use (except aztreonam, which can be used unless the reaction was to ceftazidime or aztreonam) unless approved by Allergy: organ damage (kidney, liver), drug-induced immune-mediated anemia/thrombocytopenia/leukopenia, rash with mucosal lesions (Stevens Johnson Syndrome/toxic epidermal necrosis), rash with pustules (acute generalized exanthematous pustulosis), rash with eosinophils and organ injury (DRESS – drug rash eosinophilia and systemic symptoms), rash with joint pain, fever, and myalgia (serum sickness)

⁵ Severe Sepsis: Sepsis PLUS at least 1 organ dysfunction

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- Sepsis: ≥ 2 SIRS criteria (heart rate greater than 90 bpm, respiratory rate greater than 20 breaths per minute, temperature less than 36°C , white blood count less than $4,000 \text{ cells/mm}^3$, temperature greater than 38°C , white blood count greater than $12,000 \text{ cells/mm}^3$)
 - Organ dysfunction: CV: SBP $<90 \text{ mmHg}$ or MAP $<70 \text{ mmHg}$ or require vasopressor support; Respiratory: $\text{PaO}_2/\text{FiO}_2 <250$ or mechanical ventilation; Renal: decreased urine output $<0.5 \text{ mg/kg/hr}$ for 1 hour, increased SCr ($>50\%$ from baseline); Hematologic: platelet $<100,000$ or increase aPTT; Metabolic: pH <7.3 increased lactate; Hepatic: liver enzymes $>2\text{X}$ upper limit of normal; CNS: altered consciousness
- ⁶ Shock: Sepsis induced hypotension persisting despite adequate fluid resuscitation (systolic blood pressure (SBP) $<90 \text{ mmHg}$; MAP $<70 \text{ mmHg}$; SBP decrease $>40 \text{ mmHg}$)
- ⁷ MDR-GN risk is present if any of these criteria are met: history of cefuroxime-resistant infection or colonization in prior year, history of hospitalization $>48\text{hrs}$ in prior 90 days, current hospitalization $>48\text{hrs}$, intravenous antibiotic or quinolone use within prior 90 days, significant immunocompromised, presence of an at-risk device (i.e., those deemed by the clinician to have a high risk of colonization or infection with resistant gram-negative organisms, including but not limited to *Pseudomonas aeruginosa* [e.g., central venous catheter, tracheostomy, nephrostomy/suprapubic catheter, percutaneous biliary catheter]).
- ⁸ Low-risk allergies include: pruritus without rash, remote (>10 years) unknown reaction, patient denies allergy but is on record, mild rash with no other symptoms (mild rash: non-urticarial rash that resolves without medical intervention). Medium-risk allergies include: urticaria/hives with no other symptoms, severe rash with no other symptoms (severe rash: requires medical intervention [corticosteroids, anti-histamines] and/or ER visit or hospitalization).
- ⁹ Risk factors for enterococcus in critically ill patients include septic shock, recent complex abdominal surgery, prosthetic heart valve, and recent cephalosporin or quinolone use.

This table is taken from the Michigan Medicine Antimicrobial Stewardship Committee Guidelines, and an updated electronic version is available [here](#).

Table 3: Potential Ultrasound Findings in Patients with Acute Cholecystitis

Gallbladder distention (width >4cm)
Gallbladder wall edema (wall thickness >3 mm)
Common duct dilatation (diameter >7mm) ¹
Sonographic Murphy's sign ²
Pericholecystic fluid
Gallstones and/or sludge
Sloughed mucosa
Air in the gallbladder wall

¹ Post-cholecystectomy patients may have CBD dilation in the absence of biliary pathology

² Highly operator dependent and optimally determined by a physician to exclude false-positive cases

**Table 4: Risk Stratification for the Probability of Choledocholithiasis
(Common Bile Duct Stones)**

Level	Description
Clinical predictors	
Very Strong	CBD stone on radiological imaging Clinical indication of ascending cholangitis Total bilirubin >4 mg/dL
Strong	Dilated CBD on radiological imaging (Table 1) Bilirubin 1.8 – 4 mg/dL
Moderate	Abnormal liver function test other than bilirubin Age >55 Clinical gallstone pancreatitis
Risk stratification	
High	Any “Very Strong” predictor Both “Strong” predictors
Low	No predictors from any category
Intermediate	At neither “low” nor “high” risk

EUS = endoscopic ultrasound; MRCP = magnetic resonance cholangiopancreatography.

Adapted from: ASGE Standards of Practice Committee: Maple JT, Ben-Menachem T, Anderson MA, et al. The role of endoscopy in the evaluation of suspected choledocholithiasis. *Gastrointest Endosc* 2010;71:1-9⁴

Table 5: Diagnosis of Cholangitis: Tokyo Guidelines 2018

Criteria		
A. Systemic Inflammation	Fever and/or shaking chills Laboratory data: evidence of inflammatory response (elevated WBC, CRP, etc.)	
B. Cholestasis	Jaundice (Total bilirubin ≥ 2 mg/dL) Laboratory data: abnormal liver function tests (ALP, GGT, AST and ALT)	
C. Imaging	Biliary Dilatation Evidence of the etiology on imaging (stricture, stone, stent, etc.)	
Diagnosis		
Diagnosis of Cholangitis	Suspected:	If presence of one criteria in A in addition to one item in either B or C
	Definite:	If presence of one criteria from each of A, B and C

ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; GGT: Gamma-Glutamyl Transferase.

Adapted from: Kiriya S, Kozaka K, et al. TG 2018: diagnostic criteria and severity grading of acute cholangitis. Journal of hepato-biliary-pancreatic sciences. 2018 25:17-30.⁵

Table 6: Assessment of Acute Cholangitis Severity: Tokyo Guidelines 2018 criteria

	Status	Criteria
Severity of Acute Cholangitis	Mild (Grade I)	Does not meet the criteria of “Severe” or “Moderate” acute cholangitis at time of initial diagnosis
	Moderate (Grade II)	Acute cholangitis associated with any two of the following conditions: Abnormal WBC (>12,000, <4000/mm ³) Temperature ≥39°C Age ≥75 years Hyperbilirubinemia (total bilirubin ≥5mg/dL) Hypoalbuminemia (< lower limit of normal x 0.7)
	Severe (Grade III)	Associated with onset of dysfunction in at least one of the following organs/systems: Cardiovascular dysfunction (Hypotension requiring pressors) Neurological dysfunction (Disturbance of consciousness) Respiratory dysfunction (PaO ₂ /FiO ₂ ratio <300) Renal dysfunction (Oliguria, serum creatinine >2mg/dL) Hepatic dysfunction (Elevated PT/INR >1.5) Hematological dysfunction (Platelet count <100,000/mm ³)
Assessment of the Urgency of Biliary Drainage	Urgent	Biliary drainage (<24 hours) is indicated when a. Obstructive biliary stones are associated with severe or moderate acute cholangitis – or – b. Mild acute cholangitis is not responding to IV antibiotics and fluid resuscitation – or – c. Severe (Grade III) acute cholangitis is present.
	Early (but not urgent)	ERCP (24-72 hours) is recommended for patient with mild acute cholangitis who respond to medical therapy

PT/INR = Prothrombin Time and International Normalized Ratio

Adapted from: Kiriya S, Kozaka K, et al. TG 2018: diagnostic criteria and severity grading of acute cholangitis. Journal of hepato-biliary-pancreatic sciences. 2018 25:17-30.

Table 7: Classification of Gallstone Pancreatitis: Ranson and BISAP Criteria

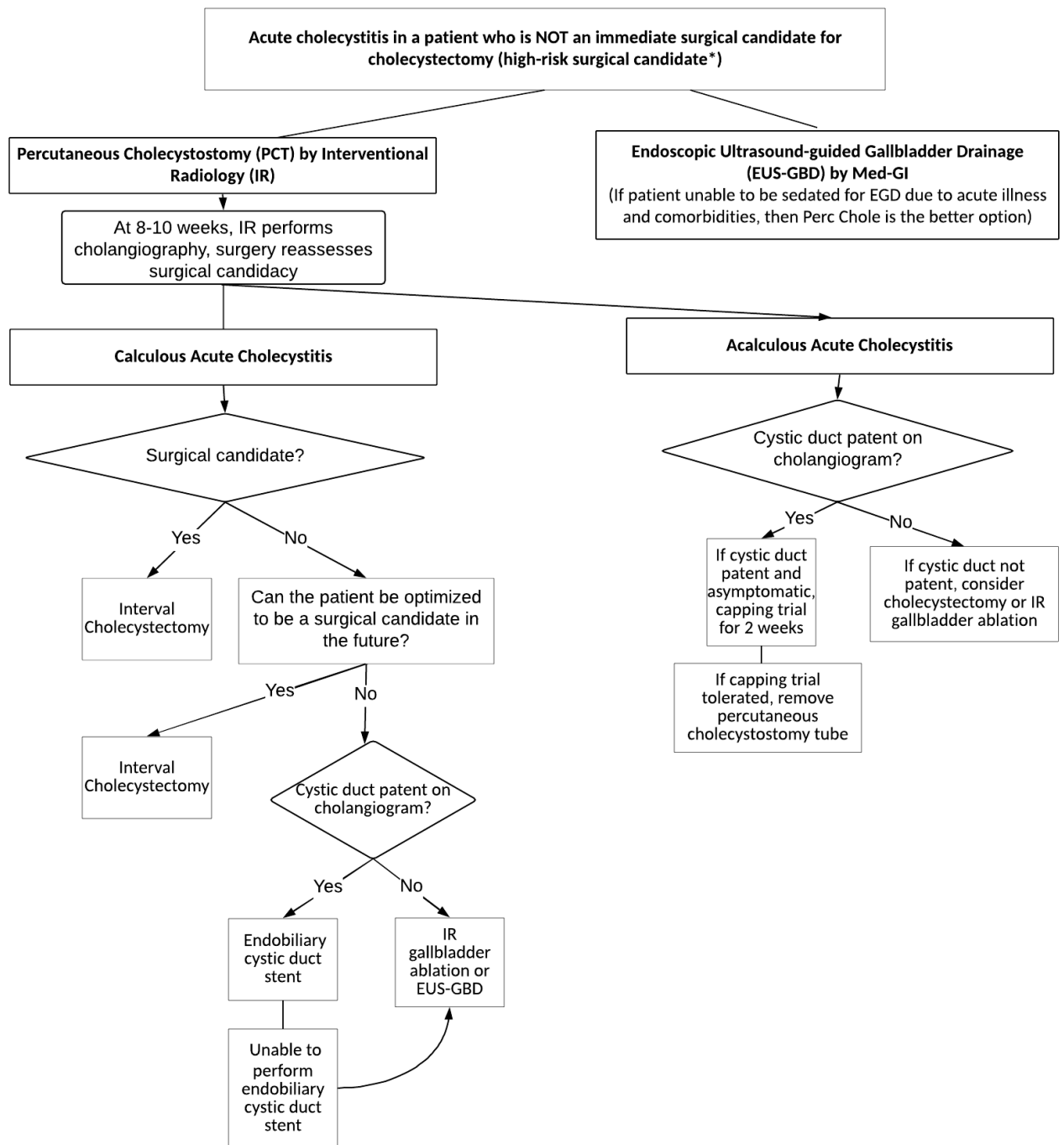
Status	Criteria
Ranson	Age >55 years Glucose >200 mg/dL LDH >350 mg/dL AST >250 units/L WBC >16 K/mm ³
BISAP	<u>B</u> UN >25 mg/dl <u>I</u> mpaired mental status (any): – disorientation, lethargy, coma, somnolence, stupor <u>S</u> IRS* <u>A</u> ge >60 years <u>P</u> leural Effusion
Severity Classification	
Mild Gallstone Pancreatitis	a. Clinical stability with admission to non-monitored bed • No significant hypovolemia • BUN <15 • HR <110 bpm b. <4 Ranson criteria or <3 BISAP Criteria on admission
Moderate to Severe Gallstone Pancreatitis	≥4 Ranson criteria on admission, or ≥3 BISAP criteria within first 24 hours of admission

AST = Aspartate aminotransferase/aspartate transaminase; BUN = Blood urea nitrogen; HR = Heart rate; LDH = Lactic dehydrogenase; SIRS = Systemic inflammatory response syndrome; WBC = White blood cell count.

*SIRS criteria = two or more of these: T >38° C OR <36°C; HR >90; RR >20 OR Pa CO₂ <32 mmHg; WBC >12,000 OR <4,000 OR >10% bands

Adapted from: Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Localio SA. Objective early identification of severe acute pancreatitis. Am J Gastroenterol 1974;61:443-51.⁶

Figure 2: Nonsurgical Management of Acute Cholecystitis



* In the DRAC-1 Trial (Teoh AYB, 2020), patients were considered high-risk for cholecystectomy if they met one of the following criteria:

- Age \geq 80 years old
- ASA Grade 3 or higher
- Age-adjusted Charlson Comorbidity Index $>$ 5
- Karnofsky score $<$ 50

Teoh AYB, Kitano M, Itoi T, Pérez-Miranda M, Ogura T, Chan SM, Serna-Higuera C, Omoto S, Torres-Yuste R, Tsuichiya T, Wong KT, Leung CH, Chiu PWY, Ng EKW, Lau JYW. Endosonography-guided gallbladder drainage versus percutaneous cholecystostomy in very high-risk surgical patients with acute cholecystitis: an international randomised multicentre controlled superiority trial (DRAC 1). Gut. 2020 Jun;69(6):1085-1091. doi: 10.1136/gutjnl-2019-319996. Epub 2020 Mar 12. PMID: 32165407.

Box 1: Downstream Management of Nonsurgical Treatment Options for Cholecystitis

For patients treated with PCT	For patients treated with EUS-GBD
<p>The PCT is maintained, in place, for 8-10 weeks, and a cholangiogram is performed. Then, one of the following options is selected:</p> <p>For patients who become surgical candidates, interval cholecystectomy is performed.</p> <p>For patients who are not surgical candidates, and have a patent cystic duct, a cystic duct stent can be placed to achieve gallbladder drainage.</p> <p>Patients who are not surgical candidates, and have obstructed cystic ducts can be treated with either IR gallbladder ablation or EUS-GBD.</p> <p>IR gallbladder ablation is a procedure in which the gallbladder is cryoablated. Gallstones are removed before the procedure, and the PCT may need to be upsized to allow for this. The ablation is performed 2 weeks after successful removal of gallstones. The PCT is then left in place for 2 weeks after the ablation procedure. A HIDA scan and a liver lab panel are performed 1 month after ablation.</p>	<p>These patients should undergo EGD for cholecystoscopy 1 month after the procedure. At this time, gallstones should be removed, and the LAMS can be replaced with a pigtail drain, or removed if the patients is doing well. If gallstones cannot be cleared during the follow-up EGD, the procedure should be repeated 1 month later. If life expectancy is short or the patient cannot tolerate additional endoscopic procedures, the LAMS is left in place, permanently.</p>

PTC = percutaneous cholecystostomy tube, EUS-GBD = endoscopic ultrasound-guided gallbladder drainage, EGD = esophagogastroduodenoscopy, LAMS = lumen-apposing metal stent

Clinical Problem and Management Issues

Gallbladder disease is common, with over 700,000 cases annually of gallstones alone in the US, and 10-15% incidence in Caucasian adults in developed countries. Risk factors for gallstones include female gender, increasing age, obesity, metabolic syndrome, and rapid weight loss.⁷

Gallstone-related disease is a common reason for hospitalization. Its management is uniquely multidisciplinary, involving emergency medicine, internal medicine, gastroenterology, radiology, and general surgery. Delays in treatment can compromise quality of care. Unnecessary testing can cause delays in treatment, raise costs, and increase length of stay.

This clinical practice guideline will enhance consistent patient management, facilitate interdisciplinary consensus, increase efficiency of patient care, and improve clinical outcomes. While not comprehensive, this guideline can guide the care of the majority of patients with gallstone-related disease.

Diagnosis

Recommendations:

- Clinical features for gallstone-related diseases are summarized in Table 1.
- Perform an evaluation that includes:
 - Complete physical exam
 - Laboratory evaluation: CBC, comprehensive metabolic panel, lipase
 - Imaging: right upper quadrant (RUQ) ultrasound
- For most patients with acute cholecystitis, make diagnosis based on history, physical findings, laboratory tests, and ultrasound (see Table 3 for the sonographic diagnostic criteria for acute cholecystitis).
- Rarely, when diagnosis is uncertain, consider additional imaging modalities.

Evaluate biliary-type pain to determine if the patient has any of the following: cholelithiasis, cholecystitis, choledocholithiasis, cholangitis, or gallstone pancreatitis. Base diagnosis of gallstone-related conditions on history and physical exam findings in combination with imaging and laboratory testing (Table 1). These conditions are not mutually exclusive and a patient may suffer from any combination of the following: cholecystitis, choledocholithiasis, cholangitis, and pancreatitis.⁸

History, Physical Exam, Signs and Symptoms

History and symptoms. Focus on the onset, pattern, and quality of the pain as well as triggering or alleviating factors. Determine the presence of anorexia, nausea, or vomiting.

Fever may or may not be present. The term “colic” may be a misnomer since patients with any of these conditions, except cholelithiasis alone, typically have constant pain that may get better or worse, but rarely resolves completely.

Physical exam and signs. No single finding or combination of physical findings establishes or excludes the diagnosis of RUQ pathology. When clinical suspicion remains, perform additional testing. Physical exam findings may include: fever, abdominal guarding or rebound, right upper quadrant mass, tenderness, Murphy’s sign, Boas’ sign, Collins’ sign, or jaundice (bilirubin >2.5 mg/dl before scleral icterus is typically seen, >5.0 before cutaneous manifestations are seen), but none are pathognomonic. Laboratory evaluation may further delineate which disease is present.

In patients who present to the emergency department with abdominal pain, clinical gestalt based on history and physical exam can raise pretest probability from 5% to 60%. Elderly patients may not exhibit classic signs and symptoms of cholecystitis, and require a high index of suspicion to avoid missing the diagnosis.⁹

Murphy’s sign. The examiner hooks his/her fingers under the right costal margin and asks the patient to inhale deeply. A test is positive if the patient stops inhaling suddenly due to pain of the gallbladder meeting the examiner’s fingers.⁸

Sonographic Murphy's sign. Performed like the Murphy's sign above, this test uses the ultrasound probe to meet the gallbladder instead of the examiner's fingers. This test may be more sensitive when performed by a radiologist (compared to the radiology technician). The physical finding is associated with gallbladder disease, although not specific for it.

Boas' sign. This sign is present when hyperesthesia exists in the right upper quadrant or right infrascapular region.

Collins' sign. This sign is present when the patient points to the right scapular tip with a fist and thumb pointing upwards to describe the pain.

Imaging

In patients with suspected gallstone-related disease, order ultrasonography (US).^{10,11} Additional imaging tests are rarely required and should only be performed in unusual situations. For example, if the initial sonogram is inconclusive or is discordant with the clinical evaluation, order cholescintigraphy. Consider computed tomography (CT) and magnetic resonance imaging (MRI) as adjunctive radiographic modalities for diagnosis of acute cholecystitis.¹² If ultrasound confirms the diagnosis, then these studies are not needed. Unnecessary CT scans and MRI increase costs and may delay definitive care, potentially complicating the course of disease. In patients at intermediate risk of choledocholithiasis, MRCP or EUS could be used to confirm the presence of CBD stones.

Right upper quadrant ultrasound. Ultrasonography of the gallbladder detects gallstones with >95% sensitivity and specificity, confers no ionizing radiation, is noninvasive, readily available, and relatively inexpensive.⁸ The liver, biliary system, and pancreas are also imaged to assess for secondary signs of gallstone-related disease suggestive of acute cholecystitis/biliary obstruction. Findings suggestive of acute cholecystitis are in Table 3. Based on a meta-analysis, the summary sensitivity and specificity of ultrasonography for acute cholecystitis are 82% and 80%.¹³

Cholescintigraphy. Reserve cholescintigraphy scanning for situations in which the initial sonogram is inconclusive or is discordant with the clinical evaluation. Also known as a HIDA scan (for 99mTc-hepatobiliary iminodiacetic acid - although other isotopes are currently in use), cholescintigraphy provides imaging-based information on gallbladder function and is superior to ultrasonography for the diagnosis of acute cholecystitis, with sensitivity of 96% and specificity of 90%.¹³ For acute cholecystitis, a "positive" HIDA equates to no gallbladder filling, which implies cystic duct occlusion.

Patients should fast for between 4-24 hours prior to cholescintigraphy. Avoid morphine and other opioid derivatives prior to imaging since they can decrease the gallbladder ejection fraction, and may lead to a potential false positive. If pain management alternatives are insufficient and opioids are required, cholecystokinin may be necessary to increase the sensitivity of the study.

Computed tomography (CT). CT is generally reserved for use when other intra-abdominal processes are suspected. Evidence is lacking to support the use of CT in the initial evaluation for gallstone-related diseases⁵ and it is not recommended as the primary modality to assess for acute cholecystitis.

Detection of gallstones on CT is poor compared to ultrasound. More than 60% of gallstones are not radiopaque and therefore, undetectable or difficult to detect. However, if CT demonstrates acute cholecystitis or choledocholithiasis, no further imaging with ultrasound is required.

Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP). MRI may be a useful alternative test for acute cholecystitis for patients in whom the US is technically degraded. Magnetic resonance imaging has become faster, more widely available, and less expensive. For MRI the summary estimate of sensitivity for acute cholecystitis is 85% with a specificity of 81%. MRI and US do not differ significantly.¹³

MRCP is a noninvasive method for detecting common bile duct stones with a negative predictive value of 100%.¹⁴ In the context of gallstone pancreatitis, MRCP may be inadequately sensitive to exclude choledocholithiasis, with a sensitivity of 62% and specificity of 98%.¹⁵

Laboratory Evaluation

Evaluate all patients presenting with suspected gallstone-related disease with laboratory testing including: a complete blood count (CBC), comprehensive metabolic panel (CMP) and lipase.

Typical historical, lab, and imaging findings for each gallstone-related clinical condition are shown in Table 1.

Biliary Colic. The white blood count, serum bilirubin, amylase, and lipase are all within a normal range.

Acute Cholecystitis. A leukocytosis with a left shift is typically present. Bilirubin, alkaline phosphatase, amylase, and lipase are not typically increased, and their elevation should provoke consideration for complicating conditions such as cholangitis or choledocholithiasis. With severe/complicated acute cholecystitis, mild elevation in bilirubin and alkaline phosphatase are possible due to inflammation of the liver bed, gallbladder perforation, and compression of the bile duct.

Choledocholithiasis. Aseptic common bile duct obstruction typically manifests with biliary pain and elevated liver enzymes (Table 1). Amylase, lipase and white blood cell count are within normal limits.

Cholangitis. As an infectious complication of biliary obstruction, cholangitis typically manifests with a leukocytosis with a left shift, elevated bilirubin >2.0 mg/dl and normal amylase and lipase.

Gallstone Pancreatitis. Amylase and lipase are typically elevated 3x above the upper limit of normal. An elevated ALT >150 suggests that the pancreatitis is of biliary origin (Table 1). Bilirubin and white blood count may not be in a normal range, depending on the location and overall burden of obstructing stones and the presence of septic complications. Note that LDH, BUN and bicarbonate are required to calculate Ranson criteria for survival in gallstone pancreatitis and should be drawn on admission. (Table 7). Calculating severity on admission helps triage patients to the appropriate level of care. A CRP level drawn 24-48 hours after admission greater than 170 mg/L predicts a 7-fold increase in hospital mortality.

Treatment

Treatment of gallstone-related disease depends on accurate diagnosis of the underlying condition. Often, these disorders coexist and treatment will need to be directed at multiple conditions simultaneously (Figure 1).

Biliary Colic

Recommendations:

- Minimally symptomatic or with symptoms that resolve:
 - Provide reassurance, education on avoidance of triggers (eg, dietary fat).
 - Refer directly to elective surgery (at University of Michigan, to General Surgery for surgery within 2 weeks).
- Moderate to severe symptoms:
 - Consult surgery
 - Consider performing non-urgent laparoscopic/open cholecystectomy during same visit.
- Timing of surgery is determined by patient preference and operating room availability.

Patients without true biliary-type pain who are diagnosed with cholelithiasis should not undergo surgery. Approximately 20% of these initially asymptomatic patients will eventually develop symptoms.¹⁶ Refer symptomatic patients for outpatient surgical consultation (at University of Michigan, General Surgery clinic

For patients with moderate to severe biliary colic, consult surgery. The majority of patients with moderate to severe biliary colic will have symptom resolution¹⁶, however, the majority eventually undergo cholecystectomy¹⁷. Therefore, consider offering laparoscopic/open cholecystectomy during the same visit. When timing surgery, consider patient preference and availability of surgical resources.

Acute Cholecystitis

Recommendations:

- In patients with acute cholecystitis, gallstones, and are candidates for surgery:
 - Initiate IV antibiotics (Table 2)

- Admit to surgery
- Perform laparoscopic/open cholecystectomy within 24-48 hours.
- In patients with acute cholecystitis, gallstones, and are not candidates for surgery:
 - Initiate IV antibiotics (Table 2)
 - Consider percutaneous cholecystostomy, cystic duct stents, or EUS guided gallbladder drainage

For patients with acute cholecystitis, perform laparoscopic/open cholecystectomy within 24 to 48 hours. Early laparoscopic/open cholecystectomy is associated with decreased length of stay and no difference in complications or conversion to open cholecystectomy compared to delayed cholecystectomy.¹⁸

Typically, antibiotics include cefuroxime 1.5 g IV every 8 hours plus metronidazole 500 mg IV/PO every 8 hours, except in cases of severe sepsis/shock, suspected multi-drug resistant gram-negative rods, or penicillin allergy (Table 2).

Occasionally, patients with acute calculous cholecystitis will be deemed high-risk for surgical intervention because of comorbid illness (Figure 1). In such cases, there are 2 major options for draining the gallbladder nonsurgically. The decision about which of these approaches is best for the patient is usually made via multidisciplinary consultation with surgery, gastroenterology, and interventional radiology. Options include the following (see Figure 2):

- **Percutaneous cholecystostomy tube (PCT).** A drainage catheter is placed into the gallbladder percutaneously. This procedure has the advantage of not requiring sedation/anesthesia, but results in an external tube.
- **EUS-guided gallbladder drainage (EUS-GBD).** A lumen-apposing metal stent (LAMS) is endoscopically placed from the gastric or duodenal lumen into the gallbladder. This procedure has the advantage of avoiding an external tube, but does require sedation/anesthesia.²⁰
- A third option is a cystic duct stent as a temporary bridge to cholecystectomy or permanent gallbladder drainage. Transpapillary gallbladder stent placement is a viable option in patients with portal hypertension who are not operative candidates,¹⁹ but it is not commonly used as a front line drainage procedure, and is more often reserved for use as a secondary procedure in patients who are treated with a cholecystostomy tube initially.

After these initial drainage procedures are performed, patients should follow up with IR, GI, and surgery to determine the next steps in management, as summarized in Box 1.

In patients without gallstones who have biliary-type pain (right upper quadrant and/or epigastric pain) and a positive hepatobiliary iminodiacetic acid (HIDA) scan showing delayed gallbladder filling or lack of gallbladder emptying, non-urgent cholecystectomy should be considered. These patients are more likely to experience symptom relief following cholecystectomy than those treated medically.²³

Acalculous cholecystitis occurs when cholecystitis is diagnosed in the absence of gallstones. This disorder is generally seen only in severely or chronically ill patients in the intensive care unit. Antibiotics and supportive care are the first-line treatments, and percutaneous cholecystostomy tubes are reserved for patients that do not improve with these initial measures. Management of cholecystostomy tubes that are placed for acalculous cholecystitis is controversial. Figure 2 summarizes the management options.

Choledocholithiasis

Recommendations:

- Evaluate for evidence of cholangitis (Table 5).
 - If cholangitis is suspected, treat as cholangitis.
 - If no evidence of cholangitis, admit to surgery and prepare for cholecystectomy.
- If choledocholithiasis is demonstrated on imaging, consider preoperative ERCP to clear the duct.
- If choledocholithiasis is not documented on imaging, estimate the likelihood of choledocholithiasis (Table 4).

- Low Likelihood: do not perform further evaluation or intraoperative cholangiography (IOC).
- Intermediate Likelihood: perform a one-stage procedure with laparoscopic/open cholecystectomy with IOC within 24 to 48 hours of admission (24 hours preferred).
 - Consider alternate approaches including: preoperative imaging with ERCP or MRCP, especially if IOC will not be performed.
 - If IOC demonstrates a retained common bile duct (CBD) stone, either perform procedure to remove CBD stones during the same operation [I-A], or obtain gastroenterology consult within 24 hours after surgery for endoscopic retrograde cholangio-pancreatography (ERCP).
- High Likelihood: preoperative ERCP is frequently performed to clear the duct.
- For patients with choledocholithiasis not amenable to the above treatments, treat with percutaneous biliary drainage.

Treat patients with concurrent cholangitis for that disorder, as outlined in the Cholangitis section below. Treatment of choledocholithiasis in the setting of biliary pancreatitis is also discussed further in the Gallstone Pancreatitis section.

Risk stratify the likelihood of choledocholithiasis based upon clinical predictors (Table 4). Treatment depends on risk.

For patients undergoing cholecystectomy with a low risk for choledocholithiasis (Table 4), do not perform routine IOC. No adequately powered studies exist to detect a decrease in CBD injury risk with routine IOC.¹⁸ Routine IOC may be associated with increased operative times and increased perioperative complication rates.¹⁹

For patients with intermediate risk of choledocholithiasis (Table 4), proceed with a cholecystectomy with an intraoperative cholangiogram. Expect ductal stones in less than 1 in 4 of these patients. If the intraoperative cholangiogram reveals evidence of choledocholithiasis, perform stone extraction either by intraoperative duct exploration or by postoperative ERCP. If IOC will not be performed, consider preoperative imaging with EUS or MRCP to further evaluate for CBD stones.

Patients with high-risk predictors for choledocholithiasis (Table 4) are typically treated with preoperative ERCP to clear the duct. However, if expertise is available to remove the CBD stones intra-operatively (surgical CBD exploration, or intra-operative ERCP), a 1-stage procedure is also a reasonable option.¹⁷

Patients with proven choledocholithiasis are usually treated with preoperative ERCP, as above. For patients who undergo ERCP as primary management for choledocholithiasis, perform cholecystectomy during the same admission (within 72 hours). Delay is associated with an increased risk of biliary events (approximately 36% within 2-6 weeks).²⁴

Even in patients with choledocholithiasis, comparison of one-stage (laparoscopic common bile duct exploration or intraoperative ERCP) versus 2-stage management (ERCP pre- or post-operatively) demonstrates no difference in ductal clearance rates, morbidity, mortality, or need for additional procedures.²⁵ One-stage management requires fewer procedures and lower cost.²⁶ Consider the risks of ERCP, including post-procedure pancreatitis (risk factors include young age and female gender). Base decisions for pre-operative ERCP on the individual patient, recognizing that risk of post-ERCP pancreatitis may delay cholecystectomy.

Patients with choledocholithiasis that is not amenable to the treatments discussed above may be treated with percutaneous biliary drainage. This treatment is addressed in the Cholangitis section.

Cholangitis

Recommendations:

- Admit to Medicine service.

- Initiate IV antibiotics, NPO (Table 2).
- Obtain Gastroenterology consult.
- Classify severity of acute cholangitis (Table 6).
 - Mild cholangitis with adequate response to medical therapy: ERCP within 72 hours.
 - Moderate-severe or not responsive to medical therapy: ERCP within 24 hours.
- Consult Surgery for laparoscopic/open cholecystectomy during same admission, after cholangitis resolves.

Choledocholithiasis is the leading etiology of acute cholangitis. Diagnostic criteria of Charcot's triad (fever, abdominal pain and jaundice) has favorable specificity, but low sensitivity for the diagnosis of cholangitis. Therefore, the presence of Charcot's triad supports the diagnosis of acute cholangitis; however, lack of these findings does not exclude the diagnosis. International guidelines for the diagnosis of acute cholangitis are summarized in Table 5.²⁷ Clinical suspicion is critical in the diagnosis of this disorder.

Although the majority of patients clinically improve with antibiotic therapy, clearing the bile duct is necessary to treat the underlying obstruction. Patients without clinical and laboratory improvement after antibiotic initiation are at risk for progression to sepsis with or without organ dysfunction. These patients require urgent biliary drainage and antibiotics. They may require intensive care unit level care.

International guidelines have graded severity of acute cholangitis as mild, moderate, or severe (Table 6). Severity assessment is critical for determining the treatment strategy for acute cholangitis.

- Severe cholangitis includes the presence of organ dysfunction and requires urgent ERCP (<24 hours).
- Moderate cholangitis risks increased severity unless urgent biliary drainage (ERCP <24 hours).
- Mild cholangitis is without hypotension or organ dysfunction and responds to medical therapy, which requires early ERCP (<72 hours).

Maintain patients admitted with cholangitis on NPO status. Perform goal directed fluid resuscitation. Start broad-spectrum antibiotics pending further evaluation with ERCP based on clinical response.

Goal directed fluid resuscitation should be administered with crystalloids (0.9% NS or LR) to goal HR <100, SBP >90 and UOP >0.5ml/kg/hr. Administer fluid boluses to meet these goals. Then administer IV fluids at a rate of 3mL/kg/hr (stipulating cardiac function that can safely tolerate this infusion rate). Patients should be managed in an intensive care unit if they require very close monitoring and/or aggressive resuscitation that cannot be accomplished on a general care unit.

Administer broad spectrum antibiotics as outlined in Table 2. Typically, antibiotics include cefuroxime 1.5 g IV every 8 hours plus metronidazole 500 mg IV/PO every 8 hours, except in cases of severe sepsis/shock, suspected multi-drug resistant gram-negative rods, or penicillin allergy.

In some cases, ERCP will be impossible because of the patient's anatomy (as in instances of Roux-en-Y anatomy), or will be unsuccessful. In these cases, urgent drainage can be achieved via percutaneous biliary drainage.

Gallstone Pancreatitis

Recommendations:

- Evaluate for evidence of cholangitis (Table 5). If suspected, treat as cholangitis (see above).
- Classify severity of gallstone pancreatitis (Table 7).
- For mild gallstone pancreatitis:
 - Admit to surgery service.
 - Perform laparoscopic/open cholecystectomy with IOC within 24 (preferred) to 48 hours.
 - If IOC demonstrates a retained CBD stone, perform surgical removal of CBD gallstone, or consult

gastroenterology for ERCP within 24 hours of surgery.

- For moderate to severe gallstone pancreatitis:
 - Admit to medicine.
 - Consider gastroenterology consultation, and preoperative ERCP if bilirubin is elevated or cholangitis present.
 - Delay cholecystectomy until pancreatitis resolves.

(For the University of Michigan, detailed management of acute pancreatitis click [here](#).)

Patients with predicted mild (Ranson criteria⁶ ≤ 3 , Table 7) gallstone pancreatitis without cholangitis, perform laparoscopic/open cholecystectomy with IOC within 48 hours. Early cholecystectomy within this group results in reduced length of the hospital stay and has not increased complications compared either to delaying cholecystectomy until resolution of abdominal pain or to normalization of laboratory values.²⁸

ERCP is not recommended routinely for preoperative patients with mild gallstone pancreatitis. Approximately 25% of these patients have CBD stones. Compared to routine preoperative ERCP, selective postoperative ERCP is associated with shorter hospital stays and no demonstrated increase in combined treatment failure rate.²⁹ Perform IOC to identify CBD stones. In patients with CBD stones, appropriate options are laparoscopic CBD exploration, intraoperative ERCP, and post-operative ERCP.

In patients with cholangitis and/or increasing bilirubin, consider pre-operative ERCP. These patients have a higher risk of persistent choledocholithiasis and may require biliary decompression via ERCP more urgently. However, patients with mild gallstone pancreatitis that undergo ERCP should still undergo cholecystectomy during the index admission. Delay of cholecystectomy in this group of patients is associated with a 14% risk of recurrent biliary events. Endoscopic sphincterotomy during ERCP reduces the risk of recurrent pancreatitis, but not of other biliary events.³⁰

This guideline does not provide detailed treatment recommendations for acute pancreatitis. (For University of Michigan, more detailed recommendations can be found at: <http://pancmap.med.umich.edu/>).

Related National Guidelines and Performance Measures

National Guidelines

The UMHS Clinical Guideline on Gallstone Related Disease is generally consistent with other guidelines published nationally and internationally, including:

Kiriyama S, Takada T, Strasberg SM, et al. TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos). *J Hepatobiliary Pancreat Sci*. 2013;20(1):24-34.

Mayumi T, Okamoto K, Takada T, et al. Tokyo Guidelines 2018: management bundles for acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci*. 2018;25(1):96-100.

National Performance Measures

At this time no major national or regional programs have clinical performance measures related to gallstone related diseases. These programs include: Centers for Medicare & Medicaid Services, National Committee for Quality Assurance: Healthcare Effectiveness Data and Information Set, Blue Cross Blue Shield of Michigan, and Blue Care Network.

Guideline Development Methodology

Funding

The development of this guideline was funded by the University of Michigan Health System (UMHS).

Guideline Development Team and Disclosures

The multidisciplinary guideline development team consisted of:

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- The medical team: Ben E. Biesterveld, MD; Hasan B. Alam, MBBS; Steven L. Kronick, MS, MD; Benjamin Pomerantz, MD; William T. Repaskey, MD; Michael D. Rice, MD
 - Guideline development methodologists: Dave Megan Mack, MD; Dave Wesorick, MD; April Proudlock, BBA, RN
 - Literature search services were provided by informationists at the Taubman Health Sciences Library, University of Michigan Medical School.

The UMHS endorses the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Contributions of team members with relevant financial relationships are reviewed by team members without relevant financial relationships to assure the information is presented without bias.

None of team members or consultants have relevant personal financial relationships.

Strategy for Literature Search

Within the Medline (Ovid) database, the following search strategy was used.

1. cholangitis/ or choledocholithiasis
2. exp cholelithiasis/ or exp cholecystitis
3. exp cholecystolithiasis/ or (exp Biliary Tract Diseases and (exp Pancreatitis/ or exp colic))
4. gallbladder or gallstone
5. cholelithiasis or cholangitis

The Main search retrieved 3,321 references. When the search hedges for Guidelines, Clinical Trials, and Cohort Studies were added, the base results are as follow:

Gallstone Related Diseases -Guidelines, total results were 176

Gallstone Related Diseases -Clinical Trials, total results were 886

Gallstone Related Diseases -Cohort Studies, total results were 2259

Within the Cochrane Database of Systematic Reviews, 23 reviews were found using the strategy in the search strategies document.

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle.

Level of evidence supporting a diagnostic method or an intervention:

A= systematic reviews of randomized controlled trials

B= randomized controlled trials

C=systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (e.g., cohort, cross-sectional, case control)

D= individual observation studies (case or case series)

E =opinion of expert panel.

Search details and evidence tables available at <http://www.uofmhealth.org/provider/clinical-care-guidelines>.

Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Health System to which the content is most relevant: Emergency Medicine, Family Medicine, General Medicine, Infectious Disease, Gastroenterology, and Radiology. Medication recommendations were reviewed by the Pharmacy and Therapeutics Committee. The final version was endorsed by the Clinical Practice Committee of the University of Michigan Faculty Group Practice and the Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers.

References

Initial Release

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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient. These recommendations are intended for UH/CVC providers.